In the Specification

**Please replace the second paragraph on page 1 of the specification with the following :**

--Nimesulide is a nonsteroidal anti-inflammatory drug (NSAID) that also has antipyretic and analgesic properties. The compound is weakly acidic (pKa = 6.5) and differs from other NSAIDs in that its chemical structure contains a sulfonanilide ~~moeity~~ moiety as the acidic group. (fig. 1) (Magni E, Nimesulide an overview, Drug Invest 1991; 3 Suppl. 2: 1-3).--

**Please replace the third paragraph on page 1 of the specification with the following :**

--The therapeutic effects of NSAIDs are largely the result of their ability to inhibit prostaglandin synthesis via inhibition of ~~cyclo-oxygenase~~ cyclooxygenase. Unfortunately, this effect is also responsible for the inhibition of gastroprotective prostaglandins, which leads to gastrointestinal intolerance.--

**Please replace the second paragraph on page 2 of the specification with the following :**

--The anti-inflammatory, analgesic and antipyretic activities of Nimesulide, a non-steroidal anti-inflammatory drug (NSAID) of the sulfonanilide class, have been demonstrated in a number of experimental models and in numerous clinical trials. Nimesulide has exhibited potency similar to or greater than that of indomethacin, diclofenac, piroxicam and ibuprofen in standard animal models of inflammation such as

~~carrageenin-induced~~ carrageenan-induced rat paw oedema and inflammation, ultraviolet light-induced erythema in guinea-pigs and adjuvant arthritis in rats. The analgesic potency in nimesulide was similar to that of ibuprofen and less than that of indomethacin in an acetic acid writhing test in rats, and acetic acid and ~~acetycholine~~ acetylcholine writhing tests in mice. Nimesulide has shown superior antipyretic potency to indomethacin, ibuprofen, aspirin and paracetamol (acetaminophen) in rats with yeast-induced fever.

Nimesulide is a relatively weak inhibitor of prostaglandin synthesis in vitro and appears to exert its effects through a variety of mechanisms including free-radical scavenging, effects on histamine release, the neutrophil ~~mycloperoxidase~~ myeloperoxidase pathway, bradykinin activity, tumour necrosis factor-α release, cartilage degradation, metalloprotease synthesis, phosphodiesterase type IV inhibition, platelet aggregation and synthesis of platelet activating factor. Animal studies have suggested that Nimesulide is less ulcerogenic than aspirin, indomethacin, naproxen, piroxicam and ibuprofen. Nimesulide appears to have little effect on renal prostaglandin synthesis in rats.--

**Please replace the second full paragraph on page 3 of the specification with the following :**

--In children, nimesulide suspension, granules and suppositories are more effective than placebo and are at least as effective as paracetamol, diclofenac, naproxen, lysine acetylsalicylate, mefenamic acid, ketoprofen and dipyrone in reducing ~~in pain~~ the pain, inflammation and fever associated with respiratory tract infection, postoperative pain and musculoskeletal injury.

Nimesulide has been well tolerated by both young and elderly adults and children in 2

large postmarketing surveillance surveys. As with other NSAIDs, the most common adverse effects are gastrointestinal disturbances (epigastralgia, heartburn, nausea, ~~diarrhoea~~ diarrhea and ~~vomiting 5.1~~ vomiting in 5.1 to 8.5% of patients), dermatological reactions (rash, pruritus; 0.2 to 0.6%) and central nervous system effects (dizziness, somnolence, headache; 0.3 to 0.4%). Withdrawal rates associated with short term (up to 30 days) nimesulide treatment range from 1.1 to 2.2% in adult, elderly and ~~paediatric~~ pediatric patients.--

**Please replace the second paragraph on page 4 of the specification with the following :**

--One approach to improve the possible non-compliance with the regimen is to develop controlled release dosage form for ~~nimesulide The~~ nimesulide. The once-a-day dosage form is expected to significantly increase the dosing convenience and patient compliance. However, controlled release once-a-day dosage form of nimesulide ~~have not~~ has not been reported so far. --

**Please replace the second paragraph on page 5 of the specification with the following :**

--One approach to formulate modified release dosage forms of NSAIDs is described in ~~U.S. Pat. No.~~ PCT Pub. No. WO9912524, wherein a unit dosage form comprising two fractions (i) a first quick release fraction, and (ii) a second fraction containing coated delayed release multiple units is described. However, such dosage forms having different fractions and coated multiple units are difficult to prepare and very cost intensive. Moreover compression of such coated multiple units into tablets cause

fracturing of the coat layer, thereby causing loss of reproducibility. --

**Please replace the third paragraph on page 5 of the specification with the following :**

~~--In U.S. Pat.~~ U.S. Pat. No. 5788987 Busetti et al. ~~describe~~ describes a time-specific controlled release dosage form. Such dosage forms are designed to provide delayed release of the active ingredient rather than extended release. Such formulations are not suitable for day long management of the disease.--

**Please replace the second paragraph on page 6 of the specification with the following:**

--Such dosage forms provide extended release of nimesulide in-vivo when given once daily with reproducible bioavailability. Further the release of such dosage forms is not ~~effected~~ affected by pH changes in the gastrointestinal system.--

**Please replace the fourth full paragraph on page 8 of the specification with the following:**

--The first fast release layer comprises materials like disintegrants, fillers, rapidly soluble/dispersible excipients and wetting agents. The second extended release layer comprises sustaining ~~polymers binders wetting~~ polymers, binders, wetting agents and fillers. --

**Please replace the second full paragraph that begins on page 9 and ends on page 11 of the specification with the following :**

--The sustaining materials comprise materials which are non-toxic and pharmaceutically acceptable. These may be natural, semi-synthetic, synthetic or man-modified. Suitable materials include cellulose and cellulose derivatives like microcrystalline cellulose, methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, cellulose carboxymethyl ethers and their salts, ~~hydroxypropyl methylcellulose~~ hydroxypropylmethyl cellulose phthalate, ~~hydroxypropyl methylcellulose~~ hydroxypropylmethyl cellulose acetate succinate.

Polyethylene; Polyquaternium-1; Polyvinyl acetate (homopolymer); Polyvinyl acetate phthalate; Propylene glycol alginate; ~~PVM/MA~~ Polyvinylmethacrylate/maleic anhydride (PVM/MA) copolymer; ~~PVP/dimethiconylacrylate/polycarbamyl/polyglycolester~~ Polyvinylpyrrolidone (PVP)/ dimethiconylacrylate/polycarbamyl/polyglycolester; ~~PVP/dimethylaminoethylm ethacrylate~~ PVP/dimethylaminoethyl methacrylate copolymer; ~~PVP/dimethylaminoethylmethacrylate/polycarbamyl~~ PVP/dimethylaminoethyl methacrylate/polycarbamyl polyglycol ester; PVP/polycarbamyl polyglycol ester; ~~PVP/VA copolymer~~ Polyvinylpyrrolidone/vinyl acetate (PVP/VA) copolymer.

Lanolin and lanolin derivatives, glyceryl monostearate, stearic acid, paraffins, beeswax, carnauba wax, Tribehenin.

Polyalkylene polyols like polyethylene glycols.
Gelatin and gelatin derivatives.

~~Alginates. Carbomers. Polycarbophils~~ Alginates, Carbomers, Polycarbophils.
Methacrylic acid copolymers.
Carrageenans, pectins, chitosans, cyclodextrins, lecithins.

Natural and synthetic gums containing galactomannans like xanthan gum, tragacanth, acacia, agar, guar gum, etc.—

**Please replace the first full paragraph on page 11 of the specification with the following:**

--Preferably the composition also comprises release modifiers. Such release modifiers are selected from the groups comprising wetting agents, solubilizers, surfactants, plasticizers, solvents, pore formers, pH modifiers and tonicity adjusting agents.--

**Please replace the third full paragraph on page 11 of the specification with the following:**

--Reaction products of natural and hydrogenated vegetable oils and ethylene glycol e.g. polyoxyethylene glycolated natural or hydrogenated castor oil such as those available under the trade name ~~Cremophor~~ Cremophor®. –

**Please replace the fourth full paragraph that begins on page 11 of the specification with the following:**

--Other suitable products include polyoxyethylene sorbitan fatty acid esters e.g. of the type available under the trade name ~~TWEEN~~ TWEEN®.
Polyoxyethylene fatty acid esters e.g. ~~MYRJ and CETIOL HE~~ MYRJ® and CETIOL®

HE.

Polyoxyethylene polyoxypropylene copolymers e.g. ~~PLURONIC~~ PLURONIC® and Polyoxyethylene polyoxypropylene block copolymers e.g. ~~POLOXAMER~~ POLOXAMER®.

Dioctylsodiumsulfosuccinate, sodium lauryl sulphate.

Propylene glycol mono- and di- fatty acid esters e.g. ~~MIGLYOL 840~~ MIGLYOL® 840.

Bile salts e.g alkali ~~metals~~ metal salts e.g. sodium taurocholate.

Polyethylene glycols, propylene glycol, triacetin, diacetin, diethyl phthalate, dibutyl phthalate, castor oil, ~~triethyl citrate dibutyl sebacate~~ triethyl citrate, dibutyl sebacate.

Sodium chloride, potassium chloride, lactose, mannitol, sucrose, sorbitol.

Sodium hydroxide, potassium hydroxide, sodium bicarbonate, sodium citrate, citric acid, hydrochloric acid, lactic acid, tartaric acid, malic acid.

The calculation of dose of nimesulide for once-a-day controlled release dosage form was done on the basis of its pharmacokinetic parameters using the following equation:--

**Please replace the second full paragraph on page 18 (Example 7) of the specification with the following:**

**--Example 7** Timed release bead type

| | | | |
|---|---|---|---|
| (i) Nimesulide (micronized) | 100 mg | 100 mg | 100 mg |
| (ii) Microcrystalline Cellulose | 200 mg | 200 mg | 200 mg |
| (iii) Lactose | 50 mg | 42 mg | 35mg |
| (iv) Polyvinyl Pyrrolidone | 10 mg | 10 mg | 10 mg |
| (v) Water | q.s | q.s | q.s |
| (vi) Ammonio Methacrylate Copolymer Type B | 10 mg | 18 mg | 25 mg |

~~(Eudragit RS)~~ (Eudragit® RS)

| | | | |
|---|---|---|---|
| (vii) Diacetin | 0.5 mg | 0.5 mg | 0.5 mg |
| (viii) Water: Acetone (1:9) | q.s | q.s | q.s |

Procedure:

In this composition 3 types of beads are prepared which are coated with different amounts of (vi) to give a timed profile of the drug. Beads are prepared by blending and ~~spheronizing (I)~~ spheronizing (i), (ii) and (iii) ~~jusing~~ using aqueous solution of (iv). The dried beads are coated with dispersion of (vi) and (vii) in (viii). The 3 different beads are blended together in a fixed ratio to obtain the required release profile.--

**Please replace the first full paragraph on page 19 (Example 8) of the specification with the following:**

**--Example 8** Nimesulide CR + Cetirizine Bilayered Tablets

Nimesulide Layer

| | | |
|---|---|---|
| (i) Nimesulide (micronized) | - | 200 mg |
| (ii) Lactose | - | 106.5 mg |
| (iii) Polyoxyl 40 Hydrogenated Castor Oil | - | 2.0 mg |
| (iv) ~~Hydroxypropylmethyl cellulose~~ Hydroxypropylmethyl cellulose | - | 31.5 mg |
| (v) Magnesium Stearate | - | 2.0 mg |
| (vi) Colloidal Silicon Dioxide | - | 2.0 mg |

Cetirizine Layer

~~(vi) Colloidal Silicon Dioxide - 2.0 mg~~

| | | |
|---|---|---|
| (vii)Cetirizine Dihydrochloride | - | 10.0 mg |
| (viii) Lactose | - | 105.0 mg |
| (ix) Microcrystalline Cellulose | - | 25.0 mg |
| (x) Starch | - | 5.0 mg |
| (xi) Croscarmellose Sodium | - | 3.0 mg |
| (xii) Magnesium Stearate | - | 2.0 mg |

Blend the components of the two layers separately and compress into bilayer tablets.--

**Please replace the first full paragraph on page 20 (Example 9) of the specification with the following :**

**Example 9 Osmotically controlled constant release system**

Active Layer

| | | | |
|---|---|---|---|
| (i) | Nimesulide (micronized) | - | 200.0 mg |
| (ii) | Polyethylene oxide | - | 116.5 mg |
| (iii) | ~~Hydroxypropylmethy cellulose~~ Hydroxypropylmethyl cellulose | - | 10.0 mg |
| (iv) | Sodium chloride | - | 10.0 mg |
| (v) | Magnesium stearate | - | 2.5 mg |

Push layer

| | | | |
|---|---|---|---|
| (vi) | Polyethylene oxide | - | 140.0 mg |
| (vii) | Sodium chloride | - | 50.0 mg |
| (viii) | Hydroxypropylmethyl cellulose | - | 9.5 mg |

| | | | |
|---|---|---|---|
| (ix) | Magnesium stearate | - | 0.5 mg |
| (x) | Iron oxide red | - | 1.0 mg |
| Functional coating | | | |
| (xi) | Cellulose acetate | - | 45.0 mg |
| (xii) | Polyethylene glycol | - | 5.0 mg |
| (xiii) | Acetone | - | Lost in processing |
| Non-functional coating | | | |
| (xiv) | Titanium dioxide | - | 2.0 mg |
| (xv) | Hydroxypropylmethyl cellulose | - | 6.0 mg |
| (xvi) | Purified Talc | - | 2.0 mg |
| (xvii) | Polyethylene glycol – 400 | - | 2.0 mg |
| (xviii) | Isopropyl Alcohol | - | Lost in processing |
| (xix) | Dichloromethane | - | Lost in processing |

Procedure: ~~Blend (I)~~ Blend (i), (ii), (iii), (iv) and (v) in a double cone blender. Separately blend (vi), (vii), (viii) (ix) and (x). Compress into bilayer tablet using a suitable compression machine. Coat the tablets with the dispersion of (xi) and (xii) in (xiii). The tablets are further coated with the dispersion of (xiv), (xv), (xvi), (xvii) in mixture of (xviii) and (xix).--

**Please replace the first full paragraph on page 21 (Example 10) of the specification with the following:**

**Example 10: Bilayer tablets having one fast release layer and one extended release layer**

Fast Release layer

| | | | |
|---|---|---|---|
| (i) | Nimesulide (micronized) | - | 100.0 mg |
| (ii) | Lactose | - | 151.5 mg |
| (iii) | Starch | - | 37.6 mg |
| (iv) | Colloidal silicon Dioxide | - | 11.0 mg |
| (v) | Povidone K-30 | - | 8.5 mg |
| (vi) | Docusate Sodium | - | 6.8 mg |
| (vii) | Polysorbate 80 | - | 1.0 g |
| (viii) | Magnesium Stearate | - | 1.6 mg |
| (ix) | Croscarmellose Sodium | - | 22.0 mg |
| (x) | Water | - | Lost in processing |

Extended Release Layer

| | | | |
|---|---|---|---|
| (xi) | Nimesulide (micronized) | - | 100.0 mg |
| (xii) | Lactose | - | 200.0 mg |
| (xiii) | Hydroxypropylmethyl cellulose K100LV | - | 23.0 mg |
| (xiv) | Hydroxypropylmethyl cellulose K4MCR | - | 100.0 mg |
| (xv) | Povidone K-30 | - | 9.0 mg |
| (xvi) | Docusate Sodium | - | 4.5 mg |
| (xvii) | Magnesium Stearate | - | 4.5 mg |
| (xviii) | Colloidal Silicon Dioxide | - | 4.5 mg |
| (xix) | Sodium Lauryl Sulphate | - | 4.5 mg |
| (xx) | Isopropyl Alcohol | - | Lost in processing |

Procedure:

Blend 1. : Blend ~~(I), (ii), (iii) and (iv)~~ (i), (ii), (iii) and (iv) and granulate with solution of (v) and (vi) in (x). Dry the granules and blend with (vii), (viii) and (ix).

Blend 2: Blend (xi), (xii), (xiii) and (xiv) and granulate with solution of ((xv) and (xvi) in (xx). Dry the granules and mix with (xvii), (xviii) and (xix).

Compress into bilayer tablets using a suitable compression machine.--

**Please replace the first full paragraph on page 22 (Example 11) of the specification with the following :**

**Example 11: Bilayer tablets having one fast release layer containing drug in complexed form and one extended release layer**

| | | | |
|---|---|---|---|
| A. | Fast Release layer | | |
| (i) | Nimesulide (micronized) | - | 100.0 mg |
| (ii) | ~~□-cyclodextrin~~ | | |
| β-cyclodextrin | | - | 400.0 mg |
| (iii) | Starch | - | 70.0 mg |
| (iv) | Povidone K-30 | - | 7.5 mg |
| (v) | Croscarmellose Sodium | - | 20.0 mg |
| (vi) | Magnesium Stearate | - | 2.5 mg |
| B. | Extended Release Layer | | |
| (vii) | Nimesulide (micronized) | - | 100.0 mg |
| (viii) | Lactose | - | 200.0 mg |
| (ix) | Hydroxypropylmethyl cellulose K100LV | - | 23.0 mg |
| (x) | Hydroxypropylmethyl cellulose K4MCR | - | 100.0 mg |
| (xi) | Povidone K-30 | - | 9.0 mg |
| (xii) | Magnesium Stearate | - | 4.5 mg |

| | | | |
|---|---|---|---|
| (xiii) | Colloidal Silicon Dioxide | - | 4.5 mg |
| (xiv) | Docusate Sodium | - | 4.5 mg |

Procedure:

Layer – I

1. Mix (i) and (ii), co-mill under specific conditions favouring complexation using ball mill to prepare a complex.
2. Mix complex of step 1 with (iii) and granulate with a solution of (iv) in water.
3. Dry the granules at 40° - 50°C.
4. Size the granules & mix with (v) and (vi)

Layer – II

1. Mix (vii), (viii), (ix) and (x). Granulate with a solution of (xi) and (xiv).
2. Dry the granules at 40° – 50°C. .
3. Size the granules & mix with (xii) and (xiii).
4. Compress the two layers into bilayered tablets using suitable compression machine.